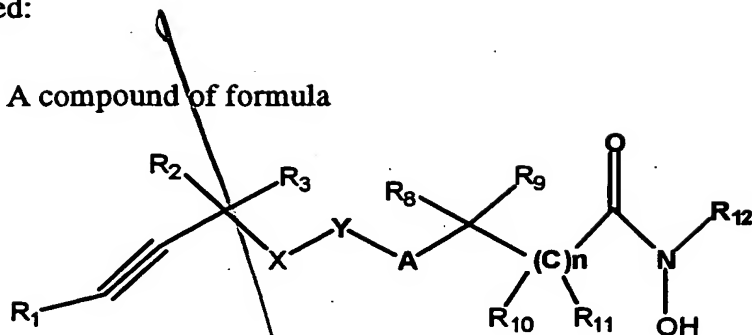


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CLAIMS

What is claimed:

1. A compound of formula



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wherein:

- 5 R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C4-C8-cycloheteroalkyl;
- 10 R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;
- 15 R_4 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)- R_1 , -SO₂- R_1 , -C(O)-NHR₁, -C(O)NR₅R₆, -C(O)R₁NR₅R₆, -C(O)-OR₁, -C(NH)-NH₂.
- 20 R_8 , R_9 , R_{10} , and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R_8 and R_9 , R_9 and R_{10} or R_{10} and R_{11} , together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of
- 25 3-6 carbon atoms, or a -C4-C8-cycloheteroalkyl ring;

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R₁₂ is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C₄-C₈-
cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO₂, NR₇, or CH₂;

X is O, S, SO, SO₂, NR₇, or CH₂;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent
atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein Y is phenyl, pyridyl, thienyl, furanyl,
imidazolyl or triazolyl or thiadiazolyl.

3. A compound of Claim 1 selected from the group consisting of:

1-(4-Bromo-benzyl)-4-(4-but-2-ynyloxy-benzenesulfonyl)-piperdine-4-
carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-methoxy-benzyl)-piperdine-4-
carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-chloro-benzyl)-piperdine-4-
carboxylic acid hydroxyamide;

1-Benzyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid
hydroxamide;

1-(4-Bromo-benzyl)-4-(4-pent-2-ynyloxy-benzenesulfonyl)-piperdine-4-
carboxylic acid hydroxyamide;

1-(4-Bromo-benzyl)-4-(4-oct-2-ynyloxy-benzenesulfonyl)-piperdine-4-
carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-fluoro-benzyl)-piperdine-4-
carboxylic acid hydroxyamide;

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- 4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-cyano-benzyl)-piperidine-4-carboxylic acid hydroxamide;
- 4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-methyl-benzyl)-piperidine-4-carboxylic acid hydroxamide;
- 5 4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(3,4-dichloro-benzyl)-piperidine-4-carboxylic acid hydroxamide;
- 1-(4-Bromo-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide;
- 1-(4-Bromo-benzyl)-4-[4-(4-piperidin-4-yl-but-2-ynyloxy)-benzenesulfonyl]-piperidine-4-carboxylic acid hydroxyamide;
- 10 1-(4-Bromo-benzyl)-4-[4-(4-morpholin-4-yl-but-2-ynyloxy)-benzenesulfonyl]-piperidine-4-carboxylic acid hydroxyamide;
- 4-(4-But-2-ynyloxy-phenylsulfanyl)-4-hydroxycarbamoyl-piperidine-1-carboxylic acid tert-butyl ester;
- 15 4-(4-But-2-ynyloxy-phenylsulfanyl)-piperidine-4-carboxylic acid hydroxyamide
- 1-(4-Bromo-benzyl)-4-(4-but-2-ynyloxy-phenylsulfanyl)-piperidine-4-carboxylic acid hydroxyamide;
- 4-(4-But-2-ynyloxy-phenylsulfanylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;
- 20 4-(4-But-2-ynyloxy-benzenesulfonylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;
- 4-(4-But-2-ynyloxy-benzenesulfinylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;
- 25 4-[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxytetrahydro-2H-pyran-4-carboxamide;
- 1-benzyl-4-[[3-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy-4-piperidine carboxamide;

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- 4-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-isopropyl-4-piperidine
carboxamide;
- 4-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-(3-pyridinylmethyl)-4-
piperidine carboxamide;
- 5 3-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-ethyl-N-hydroxy-3-piperidine-
carboxamide;
- 3-{{[4-(2-butynyloxy)phenyl]sulfonyl}-1-(4-chlorobenzyl)-N-hydroxy-3-
piperidinecarboxamide;
- 4-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-
10 piperidine-4-carboxylic acid hydroxyamide;
- 4-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-(3-pentanyl)-piperidine-4-carboxylic acid
hydroxyamide;
- 1-4-Methoxy-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-
carboxylic acid hydroxyamide;
- 15 1-(4-Chloro-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-carboxylic
acid hydroxyamide;
- tert-butyl-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-
carbonyl]-1-piperidinecarboxylate;
- 4-({[4-(But-2-ynyloxy)phenyl]thio}methyl)-N-hydroxypiperidine-4-
20 carboxamide;
- tert-Butyl-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-
carbonyl]-1-piperidinecarboxylate;
- 4-[[[4-(2-Butynyloxy)phenyl]sulfonyl]methyl]-N-hydroxy-4-piperidine-
carboxamide;
- 25 tert-Butyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-
carbonyl]piperidine-1-carboxylate;
- tert-butyl-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-
carbonyl]-1-piperidinecarboxyla;

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- 1-Acetyl-4-[[[4-(2-butynyloxy)phenyl]sulfonyl]methyl]-N-hydroxy-4-piperidinecarboxamide;
- 1-(2-Butynyl)-4-([4-(2-butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-4-piperidinecarboxamide hydrochloride;
- 5 N-1-(tert-Butyl)-4-([4-(2-butynyloxy)phenyl]sulfonyl)methyl)-N-4-hydroxy-1,4-[4-(2-butynyloxy)phenyl]sulfonyl)methyl)-N-4-hydroxy-1,4-l[sulfonyl]-methyl)-N-4--hydroxy-1,4-piperidinedicarboxamide;
- Methyl 4-([4-(2-butynyloxy)phenyl]sulfonyl)methyl)-4-[(hydroxyamino)-carbonyl]- 1-piperidinecarboxylate;
- 10 Benzyl 4-([4-(2-butynyloxy)phenyl]sulfonyl)methyl)-4-[(hydroxyamino)-carbonyl]- 1-piperidinecarboxylate;
- 1-Benzyl-4-([4-(2-butynyloxy)phenyl] sulfonyl) methyl)-N-hydroxy-4-butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-4-piperidinecarboxamide;
- 4-([4-(2-Butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-4-piperidinecarboxamide;
- 15 4-([4-(2-Butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoyl]-4-piperidinecarboxamide;
- 1-[Amino(imino)methyl]-4-([4-(2-butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-4-l]-4-([4-(2-butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-4-
- 20 oxy)phenyl]sulfonyl)methyl)-N-hydroxy-4-piperidinecarboxamide;
- 4-([4-(2-Butynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(4-hydroxy-2-butynyl)- henyl]sulfonyl)methyl)-N-hydroxy-1-(4-hydroxy-2-butynyl)-4-piperidinecarboxamide;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-1-ethyl-N-hydroxypiperidine-
- 25 4- carboxamide trifluoroacetic acid salt;
- 2-chloro-5-(chloromethyl) thiophene4-([4-(But-2-ynyloxy)phenyl]-sulfonyl)-methyl)-1-[(5-chlorothien-2-yl)methyl]-N- hydroxypiperidine-4-carboxamide trifluoroacetic acid salt;

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- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(pyridin-4-ylmethyl)piperidine-4-carboxamide trifluoroacetic acid salt;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(pyridin-3-ylcarbonyl)piperidine-4-carboxamide trifluoroacetic acid salt;
- 5 1-Benzoyl-4-([4-(but-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-piperidine-4- carboxamide;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(thien-2-ylcarbonyl) piperidine-4-carboxamide;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-1-ethyl-N-4-hydroxy-
- 10 piperidine-1,4-dicarboxamide;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-4-hydroxy-N-1- phenyl-piperidine-1,4-dicarboxamide;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-1-,N-1-diethyl-N-4-hydroxypiperidine-1,4-dicarboxamide;
- 15 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(morpholin-4-ylcarbonyl)piperidine-4-carboxamide;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-4-hydroxy-N-1-methyl-N-1-phenylpiperidine-1,4-dicarboxamide;
- Octyl-4-([4-(but-2-ynyloxy)phenyl]sulfonyl)methyl)-4-[(hydroxyamino)-
- 20 carbonyl] piperidine-1-carboxylate;
- 4-Methoxyphenyl-4-([4-(but-2-ynyloxy)phenyl]sulfonyl)methyl)-4-[(hydroxy-amino) carbonyl]piperidine-1-carboxylate;
- 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(phenylsulfonyl)piperidine-4-carboxamide;
- 25 4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]piperidine-4-carboxamide;
- 1-[2-(Benzylamino)acetyl]-4-([4-(but-2-ynyloxy)phenyl]-sulfonyl)methyl)-N-hydroxypiperidine-4-carboxamide;

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4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-(2-morpholin-4-ylacetyl)piperidine-4-carboxamide;

4-([4-(But-2-ynyloxy)phenyl]sulfonyl)methyl)-N-hydroxy-1-[2-(4-methylpiperazin-1-yl)acetyl]piperidine-4-carboxamide;

5 1-Acetyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

1-Benzoyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

10 1-(4-Methoxybenzoyl)-4-(4-but-2-ynyloxy benzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(pyrrolidine-1-carbonyl)-4-piperidinecarboxamide;

Ethyl 4-(4-but-2-ynyloxybenzenesulfonyl)-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxylate;

15 4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(trifluoromethyl)sulfonyl]-4-piperidinecarboxamide;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(3-pyridinylcarbonyl)-4-piperidinecarboxamide;

20 4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(2-thienylcarbonyl)-4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(4-methoxyphenyl)sulfonyl]-4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-4-piperidinecarboxamide;

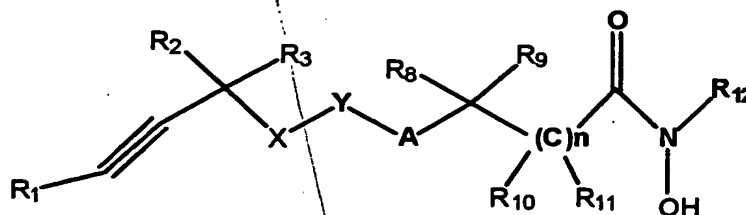
25 Tert-butyl-4-([4-(2-butynyloxy)phenyl]sulfonyl)-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxalate;

4-([4-(2-butynyloxy)phenyl]sulfonyl)-N-hydroxy-4-piperidinecarboxamide hydrochloride;

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Methyl ({4-{{4-(2-butynyloxy)phenyl}sulfonyl}-4-[(hydroxyamino)carbonyl]-
1-piperidinyl}methyl)benzoate hydrochloride;
4-({4-{{4-(2-butynyloxy)phenyl}sulfonyl}-4-[(hydroxyamino)carbonyl]-1-
piperidinyl}methyl)benzoic acid hydrochloride;
5 1-[4-(Aminocarbonyl)benzyl]-4-{{4-(2-butynyloxy)phenyl}sulfonyl}-N-
hydroxy-4-piperidinecarboxamide hydrochloride;
Tert-butyl 4-{{4-(but-2-ynyloxy)phenyl}sulfinyl}-4-[(hydroxyamino)-
carbonyl]piperidine-1-carboxalate;
4-(4-(But-2-ynyloxy-benzenesulfinyl)-piperidine-4-carboxylic acid
10 hydroxamide hydrochloride; and
1-(4-Bromo-benzyl)-4-(4-But-2-ynyloxy-benzenesulfinyl)-piperidine-4-
carboxylic acid hydroxamide hydrochloride;
and pharmaceutical salts thereof.

4. A method of inhibiting pathological changes mediated by TNF- α converting
enzyme (TACE) in a mammal in need thereof which comprises administering to said
mammal a therapeutically effective amount of a compound having the formula



wherein:

R₁ is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon
atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C₄-
C₈-cycloheteroalkyl;

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R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)- R_1 , -SO₂- R_1 , -C(O)-NHR₁, -C(O)NR₅R₆, -C(O)R₁NR₅R₆, -C(O)-OR₁, -C(NH)-NH₂.

10 R_8 , R_9 , R_{10} , and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C₄-C₈-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R_8 and R_9 , R_9 and R_{10} or R_{10} and R_{11} , together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C₄-C₈-cycloheteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C₄-C₈-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

15 A is O, S, SO, SO₂, NR₇, or CH₂;

X is O, S, SO, SO₂, NR₇, or CH₂;

20 Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

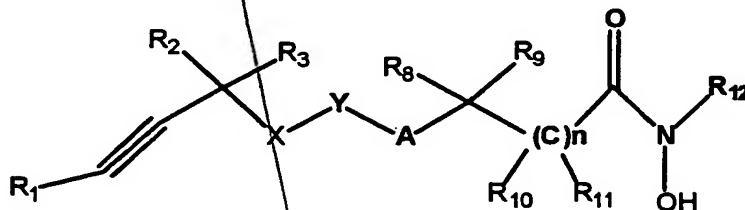
Sub
R-1

25 5. The method of Claim 4 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

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6. A pharmaceutical composition comprising a compound having the formula



wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C4-C8-cycloheteroalkyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, -C(O)- R_1 , -SO₂- R_1 , -C(O)-NHR₁, -C(O)NR₅R₆, -C(O)R₁NR₅R₆, -C(O)-OR₁, -C(NH)-NH₂.

R_8 , R_9 , R_{10} , and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R8 and R9, R9 and R10, or R10 and R11, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C4-C8-cycloheteroalkyl ring;

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Handwritten: R₁₂
R₁₂ is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C₄-C₈-
cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO₂, NR_n, or CH₂;

5

X is O, S, SO, SO₂, NR_n, or CH₂;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent
atoms of Y; and

10

n is 0-2; or a pharmaceutically acceptable salt thereof.